?ds

Set	Items	Description
S1	2006	RAB5
S2	818	RAB5 AND ENDOCYTOSIS
S3	617	S2 AND ENDOSOM?
S4	21	RAB5 AND TRANSGEN?
S5	13	RD (unique items)
S6	0	RAB5 AND ALZHEIMER'S
S7	24	RAB5 AND ALZHEIMER
S8	12	RD (unique items)
S9	25	RAB5 AND ALZHEIMER?
S10	13	RD (unique items)

?

Dialog
file: medicine
6/26/02
AmB

AMB

3/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13727894 BIOSIS NO.: 200200356715
Early endosomal **regulation of Smad-dependent signaling in endothelial cells.**
AUTHOR: Panopoulou Ekaterini; Gillooly David J; Wrana Jeffrey L; Zerial Marino; Stenmark Harald; Murphy Carol; Fotsis Theodore(a)
AUTHOR ADDRESS: (a)Laboratory of Biological Chemistry, Medical School, University of Ioannina, 45110, Ioannina**Greece E-Mail: thfotsis@cc.uoi.gr
JOURNAL: Journal of Biological Chemistry 277 (20):p18046-18052 May 17, 2002
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Transforming growth factor beta (TGFbeta) receptors require SARA for phosphorylation of the downstream transducing Smad proteins. SARA, a FYVE finger protein, binds to membrane lipids suggesting that activated receptors may interact with downstream signaling molecules at discrete endocytic locations. In the present study, we reveal a critical role for the early endocytic compartment in regulating Smad-dependent signaling. Not only is SARA localized on early **endosomes** , but also its minimal FYVE finger sequence is sufficient for early **endosomal** targeting. Expression of a SARA mutant protein lacking the FYVE finger inhibits downstream activin A signaling in endothelial cells. Moreover, a dominant-negative mutant of **Rab5** , a crucial protein for early **endosome** dynamics, causes phosphorylation and nuclear translocation of Smads leading to constitutive (i.e. ligand independent) transcriptional activation of a Smad-dependent promoter in endothelial cells. As inhibition of **endocytosis** using the K44A negative mutant of dynamin and RN-tre did not lead to activation of Smad-dependent transcription, the effects of the dominant-negative **Rab5** are likely to be a consequence of altered membrane trafficking of constitutively formed TGFbeta/activin type I/II receptor complexes at the level of early **endosomes** . The results suggest an important interconnection between early **endosomal** dynamics and TGFbeta/activin signal transduction pathways.

2002

3/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13618699 BIOSIS NO.: 200200247520
Differential endocytic functions of Trypanosoma brucei Rab5 **isoforms reveal a glycosylphosphatidylinositol-specific** endosomal **pathway.**
AUTHOR: Pal Arun; Hall Belinda S; Nesbeth Darren N; Field Helen I; Field Mark C(a)
AUTHOR ADDRESS: (a)Wellcome Trust Laboratories for Molecular Parasitology, Department of Biological Sciences and Centre for Molecular Microbiology and Infection, Imperial College of Science, Technology and Medicine, Exhibition Road, London, SW7 2AY**UK E-Mail: mfield@ic.ac.uk
JOURNAL: Journal of Biological Chemistry 277 (11):p9529-9539 March 15, 2002
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We demonstrate the presence of a glycosylphosphatidylinositol (GPI) anchor-specific **endosomal** pathway in the protozoan pathogen Trypanosoma brucei. In higher eukaryotes evidence indicates that GPI-anchored proteins are transported in both the endocytic and exocytic systems by mechanisms involving sequestration into specific membrane microdomains and consequently sorting into distinct compartments. This is potentially extremely important in trypanosomatids as the GPI anchor is the predominant mechanism for membrane attachment of surface macromolecules, including the variant surface glycoprotein (VSG). A highly complex developmentally regulated endocytic network, vital for nutrient uptake and evasion of the immune response, exists in T. brucei. In common with mammalian cells an early **endosomal** compartment is defined by **Rab5** small GTPases, which control transport processes through the **endosomal** system. We investigate the function of two trypanosome **Rab5** homologues. TbRAB5A and TbRAB5B, which colocalize in the procyclic stage, are distinct in the bloodstream form of the parasite. TbRAB5A **endosomes** contain VSG and transferrin, endocytosed by the T. brucei GPI-anchored transferrin receptor, whereas TbRAB5B **endosomes** contain the transmembrane protein ISG100 but neither VSG nor transferrin. These findings indicate the presence of trypanosome **endosomal** pathways trafficking proteins through specific routes depending on the mode of membrane attachment. Ectopic expression of mutant TbRAB5A or -5B indicates that TbRAB5A plays a role in LDL **endocytosis** , whereas TbRAB5B does not, but both have a role in fluid phase **endocytosis** . Hence TbRAB5A and TbRAB5B have distinct functions in the **endosomal** system of T. brucei. A developmentally regulated GPI-specific **endosomal** pathway in the bloodstream form suggests that specialized transport of GPI-anchored proteins is required for survival in the mammalian host.

2002

13597861 BIOSIS NO.: 200200226682

Regulation of epidermal growth factor receptor endocytosis **by wortmannin through activation of** Rab5 **rather than inhibition of phosphatidylinositol 3-kinase.**

AUTHOR: Chen Xinmei; Wang Zhixiang(a)
AUTHOR ADDRESS: (a)Department of Cell Biology and Signal Transduction Research Group, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, T6G 2H7**Canada E-Mail: zwang@cellbnt.ualberta.ca

JOURNAL: EMBO Reports 2 (9):p842-849 September, 2001
MEDIUM: print
ISSN: 1469-221X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The involvement of phosphatidylinositol 3-kinase (PI3K) in membrane trafficking in mammalian cells has largely come from experiments with wortmannin. This compound inhibits **endosome** fusion in vitro, possibly by inhibiting the production of phosphatidylinositol (PtdIns)-3-P, which co-regulates EEA1 with **Rab5** . However, the results from wortmannin inhibition experiments performed in vivo differ significantly. We have recently shown that wortmannin enlarges **endosomes** containing the epidermal growth factor receptor (EGFR) and enhances the lysosomal degradation of EGFR. In this report, we demonstrate that addition of the PI3K reaction products does not suppress wortmannin-induced enlargement of EGFR-containing **endosomes** and enhancement of EGFR degradation. Moreover, the effects of wortmannin on the intracellular trafficking of EGFR mimic those of the permanently activated **Rab5** mutant, **Rab5** Q79L, which stimulates **endosome** fusion. We also found that an inactive **Rab5** mutant, **Rab5** S34N, blocks wortmannin-induced **endosome** enlargement and that wortmannin stimulates the activation of **Rab5** . We further showed that wortmannin reduced the membrane association of p120 Ras GTPase-activating protein (GAP) and inhibited the interaction between **Rab5** and p120 Ras GAP. We conclude that wortmannin alters intracellular trafficking of EGFR by activating **Rab5** rather than by inhibiting PI3K.

2001

3/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13590813 BIOSIS NO.: 200200219634
Regulation of Trypanosoma cruzi invasion of nonphagocytic cells by the endocytically active GTPases dynamin, Rab5 , and Rab7.
AUTHOR: Wilkowsky S E; Barbieri M A; Stahl P D(a); Isola E L D
AUTHOR ADDRESS: (a)Department of Cell Biology and Physiology, Washington University School of Medicine, 660 South Euclid Avenue, Saint Louis, MO, 63110**USA E-Mail: pstahl@cellbiology.wustl.edu
JOURNAL: Biochemical and Biophysical Research Communications 291 (3):p 516-521 March 1, 2002
MEDIUM: print
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: During invasion of nonphagocytic cells by Trypanosoma cruzi (T. cruzi), host cell lysosomes are recruited to the plasma membrane attachment site followed by lysosomal enzyme secretion. The membrane trafficking events involved in invasion have not been delineated. We demonstrate here that T. cruzi invasion of nonphagocytic cells was completely abolished by overexpression of a dominant negative mutant of dynamin. Likewise, overexpression of a dominant negative mutant of **Rab5** , the rate-limiting GTPase for **endocytosis** , resulted in reduced infection rates compared with cells expressing **Rab5** wild-type. Moreover, cells expressing the activated mutant of **Rab5** experienced higher infection rates. A similar pattern was also observed when Rab7-transfected cells were examined. Confocal microscopy experiments showed that parasites colocalized with green fluorescent protein- **Rab5** -positive early **endosomes** after 5 min of invasion. These data clearly indicate that newly forming T. cruzi phagosomes first interact with an early **endosomal** compartment and subsequently with other late component markers before lysosomal interaction occurs.

2002

3/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13585389 BIOSIS NO.: 200200214210
Divalent Rab effectors regulate the sub-compartmental organization and sorting of early endosomes .
AUTHOR: De Renzis Stefano; Sonnichsen Birte; Zerial Marino(a)
AUTHOR ADDRESS: (a)Max Planck Institute for Molecular Cell Biology and Genetics, Pfotenhauerstrasse, 01307, Dresden**Germany E-Mail: zerial@mpi-cbg.de
JOURNAL: Nature Cell Biology 4 (2):p124-133 February, 2002
MEDIUM: print
ISSN: 1465-7392
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The three GTPases **Rab5** , Rab4 and Rab11 regulate sequential transport steps along the endocytic/recycling pathway, and occupy distinct membrane domains on early and recycling **endosomes** . To address the mechanisms that regulate communication between such domains, we searched for proteins that interact with both **Rab5** and Rab4. Here, we report that Rabenosyn-5, a previously identified **Rab5** effector, also binds to Rab4. Rabenosyn-5 overexpression increased the association between **Rab5** and Rab4 **endosomal** domains and decreased the fraction of Rab4- and Rab11-positive structures. This redistribution was accompanied by a faster rate of transferrin recycling from early **endosomes** to the cell surface and reduced transport to Rab11-containing perinuclear recycling **endosomes** . These effects depend on the ability of Rabenosyn-5 to interact with Rab4. We propose that divalent Rab effectors regulate protein sorting and recycling by connecting Rab domains on early **endosomes** .

2002

3/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13575124 BIOSIS NO.: 200200203945
Regulation of intracellular trafficking of the EGF receptor by Rab5 **in the absence of phosphatidylinositol 3-kinase activity.**
AUTHOR: Chen Xinmei; Wang Zhixiang(a)
AUTHOR ADDRESS: (a)Department of Cell Biology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, T6G 2H7**Canada E-Mail: zwang@cellbnt.ualberta.ca
JOURNAL: EMBO Reports 2 (1):p68-74 January, 2001
MEDIUM: print
ISSN: 1469-221X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Rab5** and phosphatidylinositol 3-kinase (PI3K) have been proposed to co-regulate receptor **endocytosis** by controlling early **endosome** fusion. However, in this report we demonstrate that inhibition of epidermal growth factor (EGF)-stimulated PI3K activity by expression of the kinase-deficient PI3K p110 subunit (p110DELTAkin) does not block the lysosomal targeting and degradation of the EGF receptor (EGFR). Moreover, inhibition of total PI3K activity by wortmannin or LY294002 significantly enlarges EGFR-containing **endosomes** and dissociates the early- **endosomal** autoantigen EEA1 from membrane fractions. However, this does not block the lysosomal targeting and degradation of EGFR. In contrast, transfection of cells with mutant **Rab5** S34N or microinjection of anti-Rabaptin5 antibodies inhibits EGFR **endocytosis** . Our results, therefore, demonstrate that PI3K is not universally required for the regulation of receptor intracellular trafficking. The present work suggests that the intracellular trafficking of EGFR is controlled by a novel **endosome** fusion pathway that is regulated by **Rab5** in the absence of PI3K, rather than by the previously defined **endosome** fusion pathway that is co-regulated by **Rab5** and PI3K.

2001

3/3,AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13547506 BIOSIS NO.: 200200176327
Expression of constitutively active Rab5 **uncouples maturation of the Salmonella-containing vacuole from intracellular replication.**
AUTHOR: Baldeon M E(a); Ceresa B; Casanova J E(a)
AUTHOR ADDRESS: (a)University of Virginia, Charlottesville, VA**USA
JOURNAL: Abstracts of the General Meeting of the American Society for Microbiology 101p52 2001
MEDIUM: print
CONFERENCE/MEETING: 101st General Meeting of the American Society for Microbiology Orlando, FL, USA May 20-24, 2001
ISSN: 1060-2011
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The enteric bacterial pathogen S. typhimurium can enter and proliferate within both phagocytic and nonphagocytic (i.e. epithelial) host cells. Upon entry, the bacteria reside in large membrane-bound vacuoles (SCV) that mature with time, as evidenced by the sequential loss of early **endosomal** markers followed by the selective recruitment of a number of lysosomal membrane glycoproteins (LAMP1, LAMP2, CD63). This maturation process is thought to be required both to prevent bacterial transport to lysosomes and to create a vacuolar environment permissive for bacterial replication. However, we have found that disruption of the endocytic pathway by expression of a constitutively active form of the small GTPase **Rab5** (Rab5Q79L) significantly altered the biogenesis of the SCV without affecting bacterial replication in HeLa cells. Expression of Rab5Q79L caused retention of early **endosomal** markers on SCVs and early acquisition of LAMP2, however, neither of these phenomena affected the kinetics of intracellular replication. We also demonstrate that a significant fraction of LAMP2 in SCVs is derived from the cell surface via **endocytosis** rather than the biosynthetic route. Further, recruitment of LAMP2 to the SCV was independent of the AP3 adaptor complex since in fibroblasts defective in AP3, where all of the newly synthesized LAMP is delivered to the cell surface, recruitment of LAMP2 to the SCVs was still evident. These findings raise the possibility that virtually all of the SCV-associated LAMP could be derived by **endocytosis** from the cell surface.

2001

AMB

5/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11491639 BIOSIS NO.: 199800272971
Effects of cytokines on mycobacterial phagosome maturation.
AUTHOR: Via L E; Fratti R A; McFalone M; Pagan-Romas E; Deretic D; Deretic V(a)
AUTHOR ADDRESS: (a)Dep. Microbiol. Immunol., Univ. Michigan, Medical Science Build. II, Ann Arbor, MI 48109**USA
JOURNAL: Journal of Cell Science 111 (7):p897-905 April, 1998
ISSN: 0021-9533
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: One of the major mechanisms permitting intracellular pathogens to parasitize macrophages is their ability to after maturation of the phagosome or affect its physical integrity. These processes are opposed by the host innate and adaptive immune defenses, and in many instances mononuclear phagocytes can be stimulated with appropriate cytokines to restrict the growth of the microorganisms within the phagosomal compartment. Very little is known about the effects that cytokines have on phagosome maturation. Here we have used green fluorescent protein (GFP)-labeled mycobacteria and a fixable acidotropic probe, LysoTracker Red DND-99, to monitor maturation of the mycobacterial phagosome. The macrophage compartments that stained with the LysoTracker probe were examined first. This dye was found to colocalize preferentially with the late endosomal and lysosomal markers rab7 and Lamp1, and with a fluid phase marker chased into the late endosomal compartments. In contrast, LysoTracker showed only a minor overlap with the early endosomal marker **rab5** . Pathogenic mycobacteria are believed to reside in nonacidified vacuoles' sequestered away from late endosomal compartments as a part of their intracellular survival strategy. We examined the status of mycobacterial phagosomes in macrophages from IL-10 knockout mice, in quiescent cells, and in mononuclear phagocytes stimulated with the macrophage-activating cytokine IFN-gamma. When macrophages were derived from the bone marrow of **transgenic** IL-10 mice lacking this major deactivating cytokine, colocalization of GFP-fluorescing mycobacteria with the LysoTracker staining appeared enhanced, suggestive of increased acidification of the mycobacterial phagosome relative to macrophages from normal mice. When bone marrow-derived macrophages from normal mice or a J774 murine macrophage cell line were stimulated with IFN-gamma and LPS, this resulted in increased colocalization of mycobacteria and LysoTracker, but no statistically significant enhancement was observed in IL-10 **transgenic** animals. These studies are consistent with the interpretation that proinflammatory and antiinflammatory cytokines affect maturation of mycobacterial phagosomes. Although multiple mechanisms are likely to be at work, we propose the existence of a direct link between cytokine effects on the host cell and phagosome maturation in the macrophage.

1998

5/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09424670 BIOSIS NO.: 199497433040
MHC class II-restricted antigen presentation in transgenic **mice expressing a** rab5 **inhibitory mutant protein.**
AUTHOR: Boretto J; Ferrier P; Naquet P; Gorvel J P; Chavrier P
AUTHOR ADDRESS: Cent. d'Immunol. INSERM-CNRS Marseille-Luminy, Case 906, 13288 Marseille Cedex 9**France
JOURNAL: Cell Biology International 18 (5):p532 1994
CONFERENCE/MEETING: IVth European Cell Biology Congress Prague, Czech

Republic June 26-July 1, 1994
ISSN: 1065-6995
RECORD TYPE: Citation
LANGUAGE: English
1994

5/3,AB/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06485063 Genuine Article#: YW263 Number of References: 59
Title: A dominant-negative mutant of the Rab5 **GTPase enhances T cell signaling by interfering with TCR down-modulation in** transgenic **mice** (ABSTRACT AVAILABLE)
Author(s): Andre P; Boretto J; Hueber AO; RegnierVigouroux A; Gorvel JP; Ferrier P; Chavrier P (REPRINT)
Corporate Source: CNRS MARSEILLE LUMINY,INSERM, CTR IMMUNOL, CASE 906/F-13288 MARSEILLE 9//FRANCE/ (REPRINT); CNRS MARSEILLE LUMINY,INSERM, CTR IMMUNOL/F-13288 MARSEILLE 9//FRANCE/; IMPERIAL CANC RES FUND,/LONDON WC2A 3PX//ENGLAND/; UNIV HEIDELBERG,/HEIDELBERG//GERMANY/
Journal: JOURNAL OF IMMUNOLOGY, 1997, V159, N11 (DEC 1), P5253-5263
ISSN: 0022-1767 Publication date: 19971201
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814
Language: English Document Type: ARTICLE
Abstract: TCR triggering results in the down-modulation of engaged receptors by endocytosis, As a result of this process, Ag-binding sites are depleted from the surface and signaling responses should be attenuated, To test the importance of TCR down-regulation on T cell signaling, we generated mice expressing a dominant-negative form of **Rab5** (Rab5N133I) in T cells, **Rab5** , a monomeric GTPase of the pas superfamily, has been implicated in the regulation of early steps in the endocytic pathway. In Rab5N133I mice, mature thymocytes developed, but the absolute number of CD4(+)CD8(+) double positive thymocytes was reduced. Fluid phase endocytosis was severely impaired in the **transgenic** thymocytes, In peripheral T cells, the kinetics and rate of ligand-induced TCR down-modulation were delayed and reduced, These effects were correlated with enhanced early and late signaling responses. Analysis of thymocyte development in doubly **transgenic** mice for Rab5N133I and a lymphocytic choriomeningitis virus (LCMV) peptide-specific TCR demonstrated that TCR signaling was enhanced by dominant inhibition of **Rab5** function, resulting in altered thymic selection, These findings suggest that TCR endocytosis is an important regulatory component of TCR signaling and that defects in this regulation can result in prolonged signaling and alter thymic development.

5/3,AB/4 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05875930 Genuine Article#: XD377 Number of References: 34
Title: Heterologous expression of rab4 reduces glucose transport and GLUT4 abundance at the cell surface in oocytes (ABSTRACT AVAILABLE)
Author(s): Mora S; Monden I; Zorzano A (REPRINT) ; Keller K
Corporate Source: UNIV BARCELONA,FAC BIOL, DEPT BIOQUIM & BIOL MOL, AVDA DIAGNAL 645/E-08028 BARCELONA//SPAIN/ (REPRINT); UNIV BARCELONA,FAC BIOL, DEPT BIOQUIM & BIOL MOL/E-08028 BARCELONA//SPAIN/; FREE UNIV BERLIN,INST PHARMAKOL/D-14195 BERLIN//GERMANY/
Journal: BIOCHEMICAL JOURNAL, 1997, V324, 2 (JUN 1), P455-459
ISSN: 0264-6021 Publication date: 19970601
Publisher: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON, ENGLAND W1N 3AJ
Language: English Document Type: ARTICLE
Abstract: To evaluate the role of the small rab GTP-binding proteins in

glucose transporter trafficking, we have heterologously co-expressed rab4 or **rab5** and GLUT4 or GLUT1 glucose transporters in Xenophus oocytes. Go-injection of rab4 and GLUT4 cRNAs resulted in a dose-dependent decrease in glucose transport; this effect was specific for rab4, since co-injection of an inactive rab4 mutant or **rab5** cRNA did not have any effect on glucose transport. The effect of rab4 was selective for GLUT4, since no effect was detected in GLUT1-expressing oocytes. The inhibitory effect of rab4 on GLUT4-induced glucose transport was not the result of a change in overall cellular levels of GLUT4 glucose transporters. However, rab4 expression caused a marked decrease in the abundance of GLUT4 transporters present at the cell surface. Finally, rab4 and inhibitors of PtdIns 3-kinase showed additive effects in decreasing glucose transport in GLUT4-expressing oocytes. We conclude that rab4 plays an important role in the regulation of the intracellular GLUT4 trafficking pathway, by contributing to the intracellular retention of GLUT4 through a PtdIns 3-kinase-independent mechanism.

5/3,AB/5 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04732589 Genuine Article#: UD840 Number of References: 27
Title: CHARACTERIZATION AND SUBCELLULAR-LOCALIZATION OF A SMALL GTP-BINDING PROTEIN (ARA-4) FROM ARABIDOPSIS - CONDITIONAL EXPRESSION UNDER CONTROL OF THE PROMOTER OF THE GENE FOR HEAT-SHOCK PROTEIN HSP81-1 (Abstract Available)
Author(s): UEDA T; ANAI T; TSUKAYA H; HIRATA A; UCHIMIYA H
Corporate Source: UNIV TOKYO,INST MOL & CELL BIOSCI,BUNKYO KU,YAYOI/TOKYO 113//JAPAN/; UNIV TSUKUBA,INST APPL BIOCHEM/TSUKUBA/IBARAKI 305/JAPAN/
Journal: MOLECULAR & GENERAL GENETICS, 1996, V250, N5 (MAR 20), P533-539
ISSN: 0026-8925
Language: ENGLISH Document Type: ARTICLE
Abstract: Small GTP-binding proteins belonging to the rab/YPT family play key roles at various steps in intracellular transport pathways in yeast and mammalian cells. Many members of rab/YPT family have been isolated from plants to date. However, detailed information about the localization and function of the gene products remains limited, even though intracellular transport is likely to be involved in important phenomena such as cell elongation, transport of storage proteins, determination and maintenance of cell polarity and intercellular signal transduction. We have attempted to establish **transgenic** Arabidopsis plants that overexpress ARA-4, a rab/YPT homologue in order to analyze the function and the localization of the gene product. For overexpression and also for regulation of the expression of this gene, the promoter of the gene for HSP81-1 was employed to drive the transcription of ARA-4 in **transgenic** plants. The response of the introduced genes to heat shock was analyzed. Upon heat-shock treatment, the ARA-4 gene was efficiently transcribed and translated. The induction of ARA-4 by heat shock was transient, and at least two distinct forms of this protein were found in membrane and cytosolic fractions from **transgenic** plants. Prolonged incubation after heat shock reduced the amount of the cytosolic form of the induced protein, and the cytosolic form of the protein thus probably represents the unprocessed precursor. Using **transgenic** plants, we determined the subcellular localization of the product of ARA-4. The protein was predominantly localized on Golgi-derived vesicles, Golgi cisternae and the trans-Golgi network.

5/3,AB/6 (Item 1 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04512177 H.W. WILSON RECORD NUMBER: BGSA01012177
Synthesis and function of 3-phosphorylated inositol lipids.

Vanhaesebroeck, Bart
Leevers, Sally J; Ahmadi, Khatereh
Annual Review of Biochemistry v. 70 (2001) p. 535-602
SPECIAL FEATURES: bibl il ISSN: 0066-4154
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 30226

ABSTRACT: The 3-phosphorylated inositol lipids fulfill roles as second messengers by interacting with the lipid binding domains of a variety of cellular proteins. Such interactions can affect the subcellular localization and aggregation of target proteins, and through allosteric effects, their activity. Generation of 3-phosphoinositides has been documented to influence diverse cellular pathways and hence alter a spectrum of fundamental cellular activities. This review is focused on the 3-phosphoinositide lipids, the synthesis of which is acutely triggered by extracellular stimuli, the enzymes responsible for their synthesis and metabolism, and their cell biological roles. Much knowledge has recently been gained through structural insights into the lipid kinases, their interaction with inhibitors, and the way their 3-phosphoinositide products interact with protein targets. This field is now moving toward a genetic dissection of 3-phosphoinositide action in a variety of model organisms. Such approaches will reveal the true role of the 3-phosphoinositides at the organismal level in health and disease. Reprinted by permission of the publisher.

5/3,AB/7 (Item 2 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04508059 H.W. WILSON RECORD NUMBER: BGSA01008059
Intracellular signaling mechanisms activated by cholecystokinin-regulating synthesis and secretion of digestive enzymes in pancreatic acinar cells.
Williams, John A
Annual Review of Physiology v. 63 (2001) p. 77-97
SPECIAL FEATURES: bibl il ISSN: 0066-4278
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 10732

ABSTRACT: The intracellular signaling mechanisms by which cholecystokinin (CCK) and other secretagogues regulate pancreatic acinar function are more complex than originally realized. CCK couples through heterotrimeric G proteins of the Gq family to lead to an increase in intracellular free Ca2+, which shows spatial and temporal patterns of signaling. The actions of Ca2+ are mediated in part by activation of a number of Ca2+-activated protein kinases and the protein phosphatase calcineurin. By the process of exocytosis the intracellular messengers Ca2+, diacylglycerol, and cAMP activate the release of the zymogen granule content in a manner that is poorly understood. This fusion event most likely involves SNARE and Rab proteins present on zymogen granules and cellular membrane domains. More likely related to nonsecretory aspects of cell function, CCK also activates three MAPK cascades leading to activation of ERKs, JNKs, and p38 MAPK. Although the function of these pathways is not well understood, ERKs are probably related to cell growth, and through phosphorylation of hsp27, p38 can affect the actin cytoskeleton. The PI3K (phosphatidylinositol 3-kinase)-mTOR (mammalian target of rapamycin) pathway is important for regulation of acinar cell protein synthesis because it leads to both activation of p70S6K and regulation of the availability of eIF4E in response to CCK. CCK also activates a number of tyrosyl phosphorylation events including that of p125FAK and other proteins associated with focal adhesions. Reprinted by permission of the publisher.

5/3,AB/8 (Item 3 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04504722 H.W. WILSON RECORD NUMBER: BGSA01004722
Protein and lipid requirements for endocytosis.
D'Hondt, Kathleen
Heese-Peck, Antje; Riezman, Howard
Annual Review of Genetics v. 34 (2000) p. 255-95
SPECIAL FEATURES: bibl il ISSN: 0066-4197
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 18765

ABSTRACT: Genetic and biochemical studies in yeast and animal cells have led to the identification of many components required for endocytosis. In this review, we summarize our understanding of the endocytic machinery with an emphasis on the proteins regulating the internalization step of endocytosis and endosome fusion. Even though the overall endocytic machinery appears to be conserved between yeast and animals, clear differences exist. We also discuss the roles of phosphoinositides, sterols, and sphingolipid precursors in endocytosis, because in addition to proteins, these lipids have emerged as important determinants in the spatial and most likely temporal specificity of endocytic membrane trafficking events. Reprinted by permission of the publisher. Reprinted by permission of the publisher.

5/3,AB/9 (Item 4 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04045918 H.W. WILSON RECORD NUMBER: BGSA99045918
AKT/PKB and other D3 phosphoinositide-regulated kinases: kinase activation by phosphoinositide-dependent phosphorylation.
Chan, Tung O
Rittenhouse, Susan E; Tsichlis, Philip N
Annual Review of Biochemistry v. 68 (1999) p. 965-1014
SPECIAL FEATURES: bibl il ISSN: 0066-4154
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 23583

ABSTRACT: The protein kinase Akt/PKB is activated via a multistep process by a variety of signals. In the early steps of this process, PI-3 kinase-generated D3-phosphorylated phosphoinositides bind the Akt PH domain and induce the translocation of the kinase to the plasma membrane where it co-localizes with phosphoinositide-dependent kinase-1. By binding to the PH domains of both Akt and phosphoinositide-dependent kinase-1, D3-phosphorylated phosphoinositides appear to also induce conformational changes that permit phosphoinositide-dependent kinase-1 to phosphorylate the activation loop of Akt. The paradigm of Akt activation via phosphoinositide-dependent phosphorylation provided a framework for research into the mechanism of activation of other members of the AGC kinase group (p70S6K, PKC, and PKA) and members of the Tec tyrosine kinase family (TecI, TecII, Btk/Atk, Itk/Tsk/Emt, Txk/Rlk, and Bm/Etk). The result was the discovery that these kinases and Akt are activated by overlapping pathways. In this review, we present our current understanding of the regulation and function of the Akt kinase and we discuss the common and unique features of the activation processes of Akt and the AGC and Tec kinase families. In addition, we present an overview of the biosynthesis of phosphoinositides that contribute to the regulation of these kinases. Reprinted by permission of the publisher.

5/3,AB/10 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13273218 22008094 PMID: 12011451

Positive selection of self-MHC-reactive T cells by individual peptide-MHC class II complexes.

Barton Gregory M; Beers Courtney; deRoos Paul; Eastman Susan R; Gomez Marcela E; Forbush Katherine A; Rudensky Alexander Y

Molecular and Cellular Biology Program, Department of Immunology, University of Washington School of Medicine, Seattle, WA 98195, USA.

Proceedings of the National Academy of Sciences of the United States of America (United States) May 14 2002, 99 (10) p6937-42, ISSN 0027-8424 Journal Code: 7505876

Contract/Grant No.: AI34206; AI; NIAID; T32 GM07270; GM; NIGMS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

If T cells require specific interactions with MHC-bound peptides during positive selection, then the specificities of T cells selected by one peptide should be distinct from those selected by another. We have examined positive selection of CD4 T cells in four strains of mice, each overexpressing a different peptide-1-A(b)(A(b)) complex. We show that a subset of CD4 T cells is selected by the overexpressed peptide and that the specificities of the CD4 T cells, as measured by reactivity to wild-type antigen-presenting cells, vary greatly depending on which peptide is overexpressed. These differences in specificity are mediated through positive selection not negative selection. Each of the four peptide-A(b) complexes appears to adopt a different conformation, and these differences correlate with the differences in reactivity. Our results suggest that individual peptide-MHC complexes positively select different subsets of self-MHC-reactive T cells and that the conformation of the peptide-MHC complex may contribute to this process.

5/3,AB/11 (Item 1 from file: 266)

00346428

IDENTIFYING NO.: 5R01NS31535-08 AGENCY CODE: CRISP

TUBEROUS SCLEROSIS GENE ON 9Q34

PRINCIPAL INVESTIGATOR: KWIATKOWSKI, DAVID J

ADDRESS: BRIGHAM AND WOMEN'S HOSPITAL 221 LONGWOOD AVE, LMRC 301 BOSTON, MA 02115

PERFORMING ORG.: BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

SPONSORING ORG.: NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

FY : 2001

SUMMARY: DESCRIPTION (Adapted from investigator's abstract): Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disease affecting 1 in 6,000 births, that is characterized by benign tumors (hamartomas and hamartias) in multiple organ systems. Its major clinical manifestations are due to brain involvement -- seizures, mental retardation and autism and related disorders, each of which occur in about half of TSC patients. The existence of two genes (TSC1 and TSC2) causing this disorder was established by familiar genetic linkage studies. TSC2 was identified 4 years ago, and has weak GTPase activating protein (GAP) activity for two members of the Ras family of GTPases, rap1 and **rab5** . In the previous application, the PI proposed to identify the TSC1 gene by positional cloning. This is now accomplished by a collaborative effort by several laboratories. There are three specific aims in the competitive renewal application: 1) A detailed mutational analysis will be performed for both the TSC1 and TSC2 loci; 2) Development of murine models of TSC; and 3)Analysis of the function of TSC1 and TSC2 proteins, hamartin and tuberin.

5/3,AB/12 (Item 2 from file: 266)

00291621

IDENTIFYING NO.: 5R01AI35884-08 AGENCY CODE: CRISP

LISTERIA MONOCYTOGENES AND PHAGOSOME MEMBRANE TRAFFIC

PRINCIPAL INVESTIGATOR: STAHL, PHILIP D

ADDRESS: WASHINGTON UNIVERSITY 660 S EUCLID AVE ST LOUIS, MO 63110

PERFORMING ORG.: WASHINGTON UNIVERSITY, ST. LOUIS, MISSOURI

SPONSORING ORG.: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

FY : 2001

SUMMARY: A wide variety of human pathogens including Listeria monocytogenes (LM) take up residence and thrive within host cells by interfering with membrane trafficking events. LM is internalized into phagosomes where it actively inhibits maturatio n of the phagosome. Virulent LM escapes to the cytoplasm. Listeria mutants (LMh ly-) that lack listeriolysin fail to access the cytoplasm but retain the ability block phagosome maturation. Newly formed phagosomes mature by dynamic remodeli ng via a series of sequential membrane fusion events followed by phagosome-lysos ome fusion. Each fusion event appears to be regulated by a RabGTPase. Rab5a is required for phagosome- endosome fusion. Live LMhly- blocks phagosome maturati on by interfering with Rab5a function. Thus, analysis of Rab5a provides an attr active opportunity to examine the regulation of phagosome maturation and the mec hanism by which LM interferes with the process. Our central hypothesis is that the GTP/GDP cycle of Rab5a is tightly coupled to phagosome maturation and the ac tivation of downstream GTPases required for efficient phagosome-lysosome fusion. Interferon gamma enhances intracellular killing of LM by selectively inducing Rab5a synthesis. Our goal is to determine how LM and Rab5a function in phagosom e maturation, to define the role of interferon gamma in facilitating the process and to delineate the role of GTPases operating down-stream including Rab7 and R ab11. The Specific Aims include identifying the signal transduction mechanisms that control the guanine nucleotide status Rab5a during phagocytosis of LM. We will also delineate the role of protein kinase B/akt, a known regulator of **Rab5** . The second specific aim focuses on the mechanism by which IFNgamma stimulates phagosome maturation and killing. Interferon gamma selectively induces Rab5a sy nthesis and processing. We will investigate the mechanism by which IFNgamma ele vates the prenylation of Rab5a. We will use phagosome-lysosome fusion assays to determine whether IFNgamma treatment enhances coupling of Rab5a to downstream R ab GTPases, Rab7 and Rab11. We will use knock out mice lacking the IFNgamma rec eptor to confirm the role played by this receptor. Since IFNgamma treatment sel ectively induces Rab5a but not Rab5b or Rab5c and since live LM causes Rab5a to accumulate on phagosomes, we will explore the possib ility that the endocytic ap paratus is composed of sub-compartments marked by different **rab5** isoforms. Rab5a may specifically connect the endocytic apparatus to the developing phagosomes w hereas other **Rab5** isoforms may have different functions. Using epitope tagged R abs coupled with both light and electron microscopy and using GFP- **Rab5** isoforms in living cells, we will identify a subset of endosomes that function in phagoso me-endosome fusion. We will use GFP- **Rab5** to observe in real time the docking an d fusion of GFP- **Rab5** isoform-marked endosomes to newly formed phagosomes harbori ng live or dead Listeria monocytogenes. We will determine the effects of IFNgam ma treatment on vesicular traffic into and out of LM phagosomes using GFP- **Rab5** , GFP-Rab7 and GFP-Rab11.

5/3,AB/13 (Item 1 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

133329618 CA: 133(24)329618p PATENT

Endocytic pathway-based methods for the identification of compounds for the treatment of Alzheimer's disease

INVENTOR(AUTHOR): Nixon, Ralph A.; Cataldo, Anne M.; Mathews, Paul M.

LOCATION: USA

ASSIGNEE: The Nathan S. Kline Institute for Psychiatric Research

PATENT: PCT International ; WO 200067016 A1 DATE: 20001109

APPLICATION: WO 2000US11401 (20000428) *US PV131890 (19990430) *US PV131991 (19990430) *US PV140643 (19990623) *US PV140644 (19990623)

PAGES: 65 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: G01N-033/00A; A01K-067/027B; A01K-067/033B; A61K-049/00B DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CR; CU; CZ; DE; DK; DM; DZ; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE ; LS; MW; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
?
?

AMB

10/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13374789 BIOSIS NO.: 200200003610
Modeling of Alzheimer **'s disease-related endocytic abnormalities affects APP metabolism.**
AUTHOR: Grbovic O M(a); Mathews P M(a); Jiang Y(a); Schmidt S D(a); Nixon R A(a); Cataldo A M
AUTHOR ADDRESS: (a)Nathan Kline Inst./NYU School of Med., Orangeburg, NY** USA
JOURNAL: Society for Neuroscience Abstracts 27 (2):p2283 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have identified endocytic pathway abnormalities as the earliest known intracellular change in sporadic **Alzheimer** 's disease (AD) and Down syndrome. We modeled aspects of these AD-related endocytic changes by overexpressing **rab5** , an important positive regulator of endocytosis, in a murine fibroblast cell line. Cells overexpressing **rab5** at low levels (2X endogenous) exhibited abnormally large **rab5** -positive early endosomes. Early endosomal antigen 1, a modulator of endosome fusion, was recruited to enlarged endosomes that were similar morphologically to those observed in AD brain. To examine alterations in APP processing, we combined metabolic labeling/immunoprecipitation with immunolabeling using various antibodies, including a novel mAb that specifically recognizes the beta-cleaved C-terminal fragment of APP (betaCTF). Cells overexpressing **rab5** showed a slight delay in APP turnover as well as increased betaCTF-specific labeling of small vesicular compartments that frequently colocalized with early endosome markers. This finding was confirmed by quantitative 125I-mAb binding, which showed increased betaCTF levels with **rab5** overexpression. Thus, in cultured cells, alterations of the early endocytic pathway that mimic those seen in human sporadic AD(1) affect APP metabolism and (2) increase betaCTF formation, presumably in an early endosomal compartment. This suggests that alterations of endocytosis in early-stage sporadic AD may directly contribute to changes in APP processing, promoting proteolysis along a beta-amyloidogenic pathway.

2001

10/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13291311 BIOSIS NO.: 200100498460
Angiotensin II type 1 a receptor intracellular trafficking is regulated by the physical association of Rab5 **.**
AUTHOR: Seachrist J L(a); Laporte S A; Anborgh P H(a); Caron M G; Ferguson S S G(a)
AUTHOR ADDRESS: (a)The John P. Robarts Research Institute, London, ON** Canada
JOURNAL: Journal of Neurochemistry 78 (Supplement 1):p146 September, 2001
MEDIUM: print
CONFERENCE/MEETING: Eighteenth Biennial Meeting of the International Society for Neurochemistry and the Thirty-Second Annual Meeting of the American Society for Neurochemistry Buenos Aires, Argentina August 26-31, 2001
ISSN: 0022-3042
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English

2001

10/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12619173 BIOSIS NO.: 200000372675
Endocytic pathway abnormalities precede amyloid beta deposition in sporadic Alzheimer 's disease and Down syndrome: Differential effects of APOE genotype and presenilin mutations.
AUTHOR: Cataldo Anne M(a); Peterhoff Corrinne M; Troncoso Juan C; Gomez-Isla Teresa; Hyman Bradley T; Nixon Ralph A
AUTHOR ADDRESS: (a)Nathan Kline Institute, 140 Old Orangeburg Road, Orangeburg, NY, 10962**USA
JOURNAL: American Journal of Pathology 157 (1):p277-286 July, 2000
MEDIUM: print
ISSN: 0002-9440
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Endocytosis is critical to the function and fate of molecules important to **Alzheimer** 's disease (AD) etiology, including the beta protein precursor (betaPP), amyloid beta (Abeta) peptide, and apolipoprotein E (ApoE). Early endosomes, a major site of Abeta peptide generation, are markedly enlarged within neurons in the **Alzheimer** brain, suggesting altered endocytic pathway (EP) activity. Here, we show that neuronal EP activation is a specific and very early response in AD. To evaluate endocytic activation, we used markers of internalization (**rab5** , rabaptin 5) and recycling (rab4), and found that enlargement of **rab5** -positive early endosomes in the AD brain was associated with elevated levels of rab4 immunoreactive protein and translocation of rabaptin 5 to endosomes, implying that both endocytic uptake and recycling are activated. These abnormalities were evident in pyramidal neurons of the neocortex at preclinical stages of disease when **Alzheimer** -like neuropathology, such as Abeta deposition, was restricted to the entorhinal region. In Down syndrome, early endosomes were significantly enlarged in some pyramidal neurons as early as 28 weeks of gestation, decades before classical AD neuropathology develops. Markers of EP activity were only minimally influenced by normal aging and other neurodegenerative diseases studied. Inheritance of the epsilon4 allele of APOE, however, accentuated early endosome enlargement at preclinical stages of AD. By contrast, endosomes were normal in size at advanced stages of familial AD caused by mutations of presenilin 1 or 2, indicating that altered endocytosis is not a consequence of Abeta deposition. These results identify EP activation as the earliest known intraneuronal change to occur in sporadic AD, the most common form of AD. Given the important role of the EP in Abeta peptide generation and ApoE function, early endosomal abnormalities provide a mechanistic link between EP alterations, genetic susceptibility factors, and Abeta generation and suggest differences that may be involved in Abeta generation and beta amyloidogenesis in subtypes of AD.

2000

10/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10774260 BIOSIS NO.: 199799395405
Amyloid protein precursor (APP) is enriched in RAB5 **-containing vesicular organelles.**
AUTHOR: Ikin A; Annaert W G; Takei K; De Camilli P; Jahn R; Greengard P; Buxbaum J D

AUTHOR ADDRESS: Rockefeller Univ., New York, NY 10021**USA
JOURNAL: Molecular Biology of the Cell 7 (SUPPL.):p326A 1996
CONFERENCE/MEETING: Annual Meeting of the 6th International Congress on Cell Biology and the 36th American Society for Cell Biology San Francisco, California, USA December 7-11, 1996
ISSN: 1059-1524
RECORD TYPE: Citation
LANGUAGE: English
1996

10/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10717247 BIOSIS NO.: 199799338392
Alzheimer **amyloid protein precursor is localized in nerve terminal preparations to** Rab5 **-containing vesicular organelles distinct from those implicated in the synaptic vesicle pathway.**
AUTHOR: Ikin Annat F; Annaert Willem G; Takei Kohji; De Camilli Pietro; Jahn Reinhard; Greengard Paul; Buxbaum Joseph D(a)
AUTHOR ADDRESS: (a)Rockefeller Univ., 1230 York Avenue, New York, NY 10021 **USA
JOURNAL: Journal of Biological Chemistry 271 (50):p31783-31786 1996
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In order to localize amyloid protein precursor (APP) in nerve terminals, we have immunoisolated vesicular organelles from nerve terminal preparations using antibodies to **Rab5** and synaptophysin. These immunoisolates were then analyzed by electron microscopy and by immunoblotting. The synaptophysin immunoisolates represented a nearly homogeneous population of small synaptic vesicles, with less than 10% contamination by other organelles, and very little APP. In contrast, **Rab5** immunoisolates contained, in addition to small synaptic vesicles, substantial numbers of large uni- and bilamellar vesicles and high levels of APP. Thus, it appears that nerve terminal APP is contained predominantly in large vesicular organelles, distinct from synaptic vesicles and from the synaptic vesicle recycling pathway.

1996

10/3,AB/6 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09117589 Genuine Article#: 368XZ Number of References: 140
Title: The endosomal-lysosomal system of neurons in Alzheimer **'s disease pathogenesis: A review** (ABSTRACT AVAILABLE)
Author(s): Nixon RA (REPRINT) ; Cataldo AM; Mathews PM
Corporate Source: NATHAN S KLINE INST PSYCHIAT RES,CTR DEMENTIA RES, 140 OLD ORANGEBURG RD/ORANGEBURG//NY/10962 (REPRINT); NYU,SCH MED, DEPT PSYCHIAT/NEW YORK//NY/10016; NYU,SCH MED, DEPT CELL BIOL/NEW YORK//NY/10016; HARVARD UNIV,MCLEAN HOSP, SCH MED/BELMONT//MA/02178
Journal: NEUROCHEMICAL RESEARCH, 2000, V25, N9-10 (OCT), P1161-1172
ISSN: 0364-3190 Publication date: 20001000
Publisher: KLUWER ACADEMIC/PLENUM PUBL, 233 SPRING ST, NEW YORK, NY 10013
Language: English Document Type: REVIEW
Abstract: A prominent feature of brain pathology in **Alzheimer** 's disease is a robust activation of the neuronal lysosomal system and major cellular pathways converging on the lysosome, namely, endocytosis and autophagy. Recent studies that identify a disturbance of the endocytic pathway as one of the earliest known manifestation of **Alzheimer** 's disease provide insight into how beta -amyloidogenesis might be promoted in sporadic **Alzheimer** 's disease, the most prevalent and

least well understood form of the disease. Primary lysosomal dysfunction has historically been linked to neurodegeneration. New data now directly implicate cathepsins as proteases capable of initiating, as well as executing, cell death programs in certain pathologic states. These and other studies support the view that the progressive alterations of lysosomal function observed during aging and **Alzheimer** 's disease contribute importantly to the neurodegenerative process in **Alzheimer** 's disease.

10/3,AB/7 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08515873 Genuine Article#: 295CU Number of References: 17
Title: Expression of the endocytosis regulatory proteins Rab5 **and Rabaptin-5 in glial cytoplasmic inclusions from brains with multiple system atrophy** (ABSTRACT AVAILABLE)
Author(s): Nakamura S (REPRINT) ; Kawamoto Y; Nakano S; Akiguchi I
Corporate Source: KYOTO UNIV,FAC MED, DEPT NEUROL/KYOTO 606//JAPAN/ (REPRINT)
Journal: CLINICAL NEUROPATHOLOGY, 2000, V19, N2 (MAR-APR), P51-56
ISSN: 0722-5091 Publication date: 20000300
Publisher: DUSTRI-VERLAG DR KARL FEISTLE, BAHNHOFSTRABE 9 POSTFACH 49, W-8024 MUNCHEN-DEISENHOFEN, GERMANY
Language: English Document Type: ARTICLE
Abstract: Background: Glial cytoplasmic inclusions (GCIs) occur specifically in oligodendrocytes in brains with multiple system atrophy (MSA). Oligodendrocytes in MSA appear to be functionally altered in their nature in terms of the occurrence of GCIs and aberrant expression of various proteins such as neuron specific protein, MAP2 or presynaptic protein, alpha-synuclein. The present study examined whether or not aberrant expression of the endocytosis regulatory proteins **Rab5** and Rabaptin-5 occur in oligodendrocytes of brains with MSA. Materials and methods: We examined immunohistochemically the post-mortem brain tissues from 5 patients with MSA and 5 controls. Immunohistochemistry was done using monoclonal anti- **Rab5** and anti-Rabaptin-5 antibodies based on ABC method. Results: We have observed **Rab5** and Rabaptin-5 immunoreactivity in the neuronal somata and axons of the controls, suggesting that **Rab5** and Rabaptin-5 are involved in the regulation of the endocytosis in neurons of the human central nervous system. In the brain tissues from patients with MSA, we have found **Rab5** and Rabaptin-5 immunoreactivity in GCIs. Conclusion: **Rab5** , in association with Rabaptin-5, has been demonstrated in the early endosome and regulates the endocytosis. Since **Rab5** and Rabaptin-5 have been immunolocalized to neurons in the human brains, we propose that oligodendrocytes may ectopically express **Rab5** and Rabaptin-5 in MSA. Thus, the oligodendrocytes in MSA brains appear to be functionally significantly altered, which may be associated with the formation of GCIs in the oligodendrocytes.

10/3,AB/8 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11304473 21347872 PMID: 11316809
Induction of neuronal cell death by Rab5A-dependent endocytosis of alpha-synuclein.
Sung J Y; Kim J; Paik S R; Park J H; Ahn Y S; Chung K C
Department of Pharmacology and Brain Research Institute, the Department of Microbiology, and the Brain Korea 21 Project for Medical Sciences, Yonsei University College of Medicine, Seoul 120-752, Korea.
Journal of biological chemistry (United States) Jul 20 2001, 276 (29) p27441-8, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed

The presynaptic alpha-synuclein is a prime suspect for contributing to Lewy pathology and clinical aspects of diseases, including Parkinson's disease, dementia with Lewy bodies, and a Lewy body variant of **Alzheimer** 's disease. Here we examined the pathogenic mechanism of neuronal cell death induced by alpha-synuclein. The exogenous addition of alpha-synuclein caused a marked decrease of cell viability in primary and immortalized neuronal cells. The neuronal cell death appeared to be correlated with the Rab5A-specific endocytosis of alpha-synuclein that subsequently caused the formation of Lewy body-like intracytoplasmic inclusions. This was further supported by the fact that the expression of GTPase-deficient Rab5A resulted in a significant decrease of its cytotoxicity as a result of incomplete endocytosis of alpha-synuclein.

10/3,AB/9 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10296089 99274681 PMID: 10341289

Differential involvement of small G proteins in Alzheimer **'s disease.**

Shimohama S; Kamiya S; Taniguchi T; Sumida Y; Fujimoto S

Department of Neurology, Graduate School of Medicine, Kyoto University, Sakyoku, Kyoto 606-8507, Japan.

International journal of molecular medicine (GREECE) Jun 1999, 3 (6) p597-600, ISSN 1107-3756 Journal Code: 9810955

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Alzheimer 's disease (AD) is a neurodegenerative disease characterized by the progressive deterioration of cognitive function and memory in association with the wide-spread presence of senile plaques, neurofibrillary tangles and neuronal cell death. However, its pathophysiology remains unknown. GTP-binding proteins with molecular weights of approximately 20,000 are designated small G proteins. In the present study we quantitatively analyzed the small G proteins, Ras, Rap, Ral and Rab in brains removed at autopsy from controls and AD patients to examine whether small G proteins are equally or differentially affected in AD. Western blot analysis indicated that the protein level of Ras and RalB in both the cytosolic and membranous fractions and that of Rap2 in the cytosolic fraction was significantly decreased, while that of Rab8 in the membranous fraction was significantly increased in AD brains compared with controls. The protein level of other small G proteins was not different between control and AD brains. These results suggest a differential involvement of small G proteins in AD.

10/3,AB/10 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09799019 98244764 PMID: 9585365

Neuropathology of preclinical and clinical late-onset Alzheimer **'s disease.**

Troncoso J C; Cataldo A M; Nixon R A; Barnett J L; Lee M K; Checler F; Fowler D R; Smialek J E; Crain B; Martin L J; Kawas C H

Alzheimer's Disease Research Center, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21205-2196, USA.

Annals of neurology (UNITED STATES) May 1998, 43 (5) p673-6, ISSN 0364-5134 Journal Code: 7707449

Contract/Grant No.: AG05146; AG; NIA; AG10916; AG; NIA

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We report on the neuropathological examinations of a 74-year-old woman with **Alzheimer** 's disease (AD) and of her 47-year-old nondemented daughter. The brain of the mother showed fully developed pathological

changes of AD. By contrast, the brain of the daughter revealed only perineuronal deposition of diffuse amyloid in cerebral cortex and striking abnormalities of the endosomal-lysosomal system, without neurofibrillary, glial, or microglial changes. These observations suggest that amyloid deposition and endosomal-lysosomal changes are early events in late-onset AD and that they may precede the onset of dementia by several decades.

10/3,AB/11 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09476138 97383265 PMID: 9236226
Increased neuronal endocytosis and protease delivery to early endosomes in sporadic Alzheimer **'s disease: neuropathologic evidence for a mechanism of increased beta-amyloidogenesis.**
Cataldo A M; Barnett J L; Pieroni C; Nixon R A
Laboratories for Molecular Neuroscience, McLean Hospital, Belmont, Massachusetts 02178, USA.
Journal of neuroscience : the official journal of the Society for Neuroscience (UNITED STATES) Aug 15 1997, 17 (16) p6142-51, ISSN 0270-6474 Journal Code: 8102140
Contract/Grant No.: 5R35 AG10916-05; AG; NIA; MH/NS31862; MH; NIMH
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The early endosome is the first vacuolar compartment along the endocytic pathway. It is the site of internalization and initial processing of amyloid precursor protein (APP) and apolipoprotein E (ApoE), two proteins of etiological importance in **Alzheimer** 's disease, and a putative site of beta-amyloid peptide (Abeta) formation. Here, we identify early endosomes in human pyramidal neurons, using specific compartmental markers and morphometry, and show that in **Alzheimer** 's disease individual endosomes display up to 32-fold larger volumes than the normal average. Endosomal enlargement contributed to an average 2.5-fold larger total endosomal volume per neuron, implying a marked increase in endocytic activity. Endosomal alterations were evident in most pyramidal neurons in **Alzheimer** brain, detectable at early stages of the disease but absent in several other neurodegenerative disorders examined. In addition, mature and proenzyme forms of the proteases cathepsin B and cathepsin D, a candidate APP secretase, were identified in most early endosomes in **Alzheimer** brains but were detectable in only a minor proportion of endosomes in normal brain. Expression of the cation-dependent 46 kDa mannose 6-phosphate receptor was elevated in pyramidal neurons of **Alzheimer** brains, which could be a possible basis for the altered cathepsin trafficking pattern. Enhanced endocytic activity, coupled with increased trafficking to endosomes of proteases, which may have the ability under pathological conditions to generate Abeta, constitutes a potential mechanism by which beta-amyloidogenesis may become accelerated in sporadic AD and also be subject to influences by ApoE.

10/3,AB/12 (Item 1 from file: 266)
DIALOG(R)File 266:FEDRIP

00288191
IDENTIFYING NO.: 5R01AG14996-04 AGENCY CODE: CRISP
RAB5 **AND APP PROCESSING AS RELATED TO AGING**
PRINCIPAL INVESTIGATOR: BUXBAUM, JOSEPH D
ADDRESS: MOUNT SINAI SCH OF MEDICINE ONE GUSTAVE L LEVY PL, BOX 123 NEW YORK, NY 10029
PERFORMING ORG.: MOUNT SINAI SCHOOL OF MEDICINE OF NYU, NEW YORK, NEW YORK
SPONSORING ORG.: NATIONAL INSTITUTE ON AGING
FY : 2001
SUMMARY: DESCRIPTION A preponderance of evidence suggests that neurons

are a major source of Abeta in the brain. Little is known about the subcellular localization and processing of APP in central neurons, although it is known that APP undergoes both anterograde and retrograde transport. It is also known that APP is not found in appreciable amounts in neuronal plasma membranes. The fate of transported APP is therefore still a mystery. In preliminary studies the PI has been able to demonstrate that a majority of APP in synapses is found in a novel, **rab5** -rich, vesicular organelle. **Rab5** is a small GTP-binding protein which is required for endocytosis in fibroblasts and is involved in the recycling of small synaptic vesicles in nerve terminals. The major focus of this application will be the further purification and characterization of this organelle, the determination of the role of **rab5** (and other APP-associated proteins) in APP trafficking and processing, and the characterization of the novel organelle as a potential site of APP metabolism. Specific Aim 1: To localize APP within highly purified synaptosomes (containing nerve terminals and some postsynaptic elements), and purify and characterize the APP-containing synaptic organelles by conventional and/or immunological methods. Specific Aim 2: To determine the ability of specific proteins, associated with APP-containing synaptic organelles, to regulate the localization, trafficking, and processing of APP in cultured cells, including polarized epithelial cells and primary neuronal cultures. Specific Aim 3: To test the purified APP-containing synaptic organelles for their ability to metabolize APP and for the presence of proteases, including the a-secretase that the PI has recently identified, as well as for the presence of the **Alzheimer** -associated proteins, presenilin-1, presenilin-2, and apolipoprotein E.

10/3,AB/13 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

133329618 CA: 133(24)329618p PATENT
Endocytic pathway-based methods for the identification of compounds for the treatment of Alzheimer's disease
INVENTOR(AUTHOR): Nixon, Ralph A.; Cataldo, Anne M.; Mathews, Paul M.
LOCATION: USA
ASSIGNEE: The Nathan S. Kline Institute for Psychiatric Research
PATENT: PCT International ; WO 200067016 A1 DATE: 20001109
APPLICATION: WO 2000US11401 (20000428) *US PV131890 (19990430) *US PV131991 (19990430) *US PV140643 (19990623) *US PV140644 (19990623)
PAGES: 65 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: G01N-033/00A; A01K-067/027B; A01K-067/033B; A61K-049/00B DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CR; CU; CZ; DE; DK; DM; DZ; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE ; LS; MW; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
?